Article

Survival and echocardiographic data in dogs with congestive heart failure caused by mitral valve disease and treated by multiple drugs: A retrospective study of 21 cases

Eric de Madron, Jonathan N. King, Günther Strehlau, Regina Valle White

Abstract — This retrospective study reports the survival time [onset of congestive heart failure (CHF) to death from any cause] of 21 dogs with mitral regurgitation (MR) and CHF treated with a combination of furosemide, angiotensin-converting enzyme inhibitor (ACEI, benazepril, or enalapril), pimobendan, spironolactone, and amlodipine. Baseline echocardiographic data: end-systolic and end-diastolic volume indices (ESVI and EDVI), left atrium to aorta ratio (LA/Ao), and regurgitant fraction (RF) are reported. Median survival time (MST) was 430 d. Initial dosage of furosemide (P = 0.0081) and LA/Ao (P = 0.042) were negatively associated with survival. Baseline echocardiographic indices (mean ± standard deviation) were 40.24 ± 16.76 for ESVI, 161.48 ± 44.49 mL/m^2 for EDVI, 2.11 ± 0.75 for LA/Ao, and 64.71 ± 16.85% for RF. Combining furosemide, ACEI, pimobendan, spironolactone, and amlodipine may result in long survival times in dogs with MR and CHF. Severity of MR at onset of CHF is at least moderate.

Résumé — Données sur la survie et l'échocardiographie chez des chiens avec une insuffisance cardiaque congestive causée par une maladie des valvules mitrales et traitée à l'aide de médicaments multiples : étude rétrospective de 21 cas. Cette étude rétrospective fait rapport sur le temps de survie [depuis l'apparition de l'insuffisance cardiaque congestive (ICC) jusqu'à la mort d'une cause quelconque] de 21 chiens avec une régurgitation mitrale (RM) et l'ICC traitée avec une combinaison de furosémide, d'inhibiteur d'enzyme de conversion de l'angiotensine (ACEI, benazepril ou enalapril), de pimobendan, de spironolactone et d'amlodipine. Les données de référence échocardiographiques suivantes sont rapportées : indices de volume ventriculaire en fin de télédiastole et de diastole (ESVI et EDVI), ratio de l'oreillette gauche à l'aorte (LA/Ao) et fraction de régurgitation (FR). La durée médiane de survie était de 430 jours. La dose initiale de furosémide (P = 0,0081) et le LA/Ao (P = 0,042) était négativement associée à la survie. Les indices de référence de l'échocardiographie (moyenne ± écart-type) étaient de 40,24 ± 16,76 pour ESVI, de 161,48 ± 44,49 mL/m^2 pour EDVI, de 2,11 ± 0,75 pour LA/Ao et de 64,71 ± 16,85 % pour RF. La combinaison de furosémide, d'ACEI, de pimobendan, de spironolactone et de l'amlodipine pourrait entraîner des durées de survie plus longues chez les chiens atteints de RM et d'ICC. La gravité de RM à l'apparition de l'ICC est au moins modérée.

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Introduction

Mitral regurgitation (MR) secondary to myxomatous degenerative mitral valve disease (DMVD) is the most common heart disease and cause of heart failure in dogs (1,2). Once dogs have developed congestive heart failure (CHF), most die within 6 to 14 mo after the appearance of clinical signs (3,4). Treatment of dogs with CHF secondary to DMVD typically consists of a loop-diuretic (furosemide) and additional agents (1,2).

The angiotensin-converting enzyme inhibitors (ACEIs) benazepril and enalapril, when combined with furosemide, significantly prolong survival and time to withdrawal from the study in dogs with CHF caused by DMVD. This combination also improves their quality of life (3–6). The inodilator pimobendan has been evaluated in humans with CHF due to systolic dysfunction (7,8), and more recently in dogs with CHF due to either dilated cardiomyopathy (DCM) or DMVD

Alta Vista Animal Hospital, 2616 Bank Street, Ottawa, Ontario K1T 1M9 (de Madron, White); Novartis Animal Health Inc, Clinical Development, CH-4058, Basel, Switzerland (King, Strehlau).

Address all correspondence to Dr. Eric de Madron; e-mail: ericdem@magma.ca

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(9–13). Several studies have compared dogs with DMVD receiving pimobendan and furosemide versus dogs receiving an ACEI (ramipril or benazepril) and furosemide (11–13). Dogs showed an improvement in clinical signs and quality of life, and a reduction of the likelihood of developing an adverse cardiac event. Dogs receiving pimobendan survived longer than dogs not receiving it in the VetSCOPE and QUEST studies (12,13).

Spironolactone, an aldosterone antagonist with mild diuretic effects, substantially improves survival when added to standard cardiac therapy in humans with chronic CHF and low ejection fraction (14). Improved survival and reduction of risk for a cardiac event have recently been shown in dogs with DMVD and CHF (15). Amlodipine, a calcium channel blocker, has been shown in a pilot study to reduce the volume of MR, regurgitant orifice area, and left ventricle (LV) end-diastolic diameter in dogs, presumably by decreasing the systolic left ventricular pressure (16).

The current guidelines for the treatment of dogs with CHF secondary to chronic DMVD recommend the combination of drugs including at least furosemide, an ACEI, and pimodendan (17). Other drugs such as spironolactone and amlodipine may also be of benefit. However, the superiority of combination therapy over furosemide and pimobendan alone has not been documented.

The main goal of this retrospective study was to report the survival characteristics of a population of dogs with similar inclusion criteria with the dogs used in the QUEST study, which were treated in a systematic fashion with a combination of drugs including furosemide, an ACEI (benazepril or enalapril), pimobendan, amlodipine, and spironolactone. A secondary goal was to report some echocardiographic parameters at the onset of CHF, to better understand the degree of MR severity, and the inotropic state of the left ventricle at that time.

Materials and methods

Study population

The medical records of dogs examined at the Alta Vista Animal Hospital in Ottawa, Ontario between January 1, 2003 and July 1, 2008 for evaluation of a heart murmur and presence of clinical signs of CHF were reviewed. From these records, 44 cases diagnosed with primary DMVD and documented CHF requiring furosemide for stabilization were identified. Out of these initial 44 cases, 21 cases that met the following inclusion and exclusion criteria were selected (in order to be comparable with the results from the QUEST study).

Inclusion criteria

All dogs included in the study had to have undergone physical, radiographic, and echocardiographic examinations. The dogs had to weigh between 5 and 20 kg, to be at least 5 years old, and have a systolic murmur with the maximum point of intensity over the mitral valve area. The presence of pulmonary edema had to be documented by pulmonary infiltrates and left atrial dilation on thoracic radiographs, clinical signs of dyspnea or cough or both, and the need for furosemide to stabilize these clinical signs. Adjunct treatment had to include at least an ACEI (benazepril or enalapril), pimobendan, spironolactone, and amlodipine. Echocardiographic inclusion criteria included anomalies of the mitral valve leaflets (prolapse, thickening) and the presence of mitral valve regurgitation on color Doppler examination. The left ventricular shortening fraction (SF) had to be $>$ 20%. Dogs with tricuspid insufficiency attributable to pulmonary hypertension were included if this was judged to be secondary to DMVD. Finally, the owners had to be available for follow-up telephone interviews, in order to collect survival data.

Table 1. Clinical and echocardiographic data for 21 dogs with chronic heart failure secondary to degenerative mitral valve disease

	Mean	Standard deviation	Minimum	Maximum
Age (y)	10.38	2.36	6	16
Weight (kg)	9.64	3.89	5.8	19.3
VHS	11.63	0.87	10.5	13
SBP (mmHg)	125	18.21	102	172
EDVI (mL/m^3)	161.5	44.5	80.5	235.6
ESVI (mL/m^3)	40.24	16.76	15.36	80.41
LA/Ao	2.11	0.75	1.4	4.5
SF%	43.54	9.02	29.3	60
RF%	64.71	16.85	32.2	85.2

VHS — radiographic vertebral score; SBP — systolic arterial blood pressure; EDVI — end-diastolic volume indices; ESVI — end-systolic volume indices; LA/Ao — left atrium aorta ratio; SF% — shortening fraction; RF% — regurgitant fraction.

Exclusion criteria

Dogs with severe systolic dysfunction (SF $<$ 20%), or with concomitant congenital or acquired heart disease, such as aortic regurgitation due to bacterial endocarditis, were excluded.

Baseline data

The following data were obtained from the medical records: age, body weight, gender, systolic arterial blood pressure (SBP), presence of CHF (pulmonary edema detected on thoracic radiographs), radiographic vertebral score (VHS), and baseline treatment (drugs and dosages). Blood pressure was measured noninvasively by Doppler sphygmomanometry or oscillometry. The following echocardiographic data were retrieved: end-diastolic and end-systolic volume indexes (EDVI and ESVI), SF, left atrial to aortic root ratio (LA/Ao) and the regurgitant volume using the proximal isovelocity surface area (PISA) method. All clinical datasets were reviewed by a single board-certified cardiologist (EDM).

Echocardiography

Echocardiographic examination, performed on an ALOKA SSD 4000 (Imago Solutions Médicales, Vaudreuil — Dorion, Quebec), included transthoracic 2-D, M-mode, spectral, and color flow Doppler. Transducer arrays of 5.0–7.5 and 2.5–3.5 MHz were used. Examinations were performed in conscious, unsedated dogs. Right parasternal M-mode recordings were obtained from short-axis views with the dogs positioned in right lateral recumbency, and the 2-D echocardiograms were obtained in accordance with techniques described elsewhere (18–20). The presence of mitral valve regurgitation was evaluated by color Doppler in the right parasternal long-axis and left apical views.

Table 2. End-systolic volume index at onset of chronic heart failure (CHF) in 21 dogs with CHF secondary to degenerative mitral valve disease (DMVD)

ESVI	Normal (< 30 mL/m^2)	Mildly elevated (30 to 40 mL/m^2)	Moderately elevated (41 to 70 mL/m^2)	Severely elevated (> 70 mL/m^2)
n	5	5	10	1
%	24%	24%	48%	5%

ESVI — end-systolic volume indices.

All echocardiographic measurements were made by the same investigator (EDM). The EDVI and ESVI were calculated using the Teichholz method (20). Values of ESVI > 30 mL/m^2 were considered indicative of systolic dysfunction (30 to 40–mild; 41 to 70–moderate, and > 70–severe). The regurgitant fraction (RF) of the mitral regurgitation was calculated using the regurgitant volume obtained with the PISA method (MR volume) as described elsewhere, and the aortic stroke volume derived from the velocity time integral of the aortic flow spectral Doppler signal (SVAo), using the formula:

RF(%) = MR volume/(MR volume + SVAo) (21,22)

The pressure gradient between the right ventricle and the right atrium was derived from the maximal tricuspid regurgitation jet velocity (23). Pulmonary hypertension was deemed to be present if this gradient was > 30 mmHg.

Survival

The clinical progress of each dog was ascertained by telephone interviews with the owner. The interviews were conducted by a specifically trained student (RVW) who was not blinded to the clinical status of the dog at the initial examination. The owner was asked if the dog was dead or alive. If the dog was dead, the owner was asked if the dog had been euthanized or died spontaneously, and reasons for euthanasia. In case of spontaneous death, the possible causes, including cardiac-related sudden death, presence of syncope, or progression of heart failure (HF) were probed. Cardiac-related death was defined as death occurring because of progression of clinical signs of HF. Euthanasia because of refractory HF was scored as cardiac-related death. Sudden death was regarded as cardiac-related if no other cause of death was obvious. Survival analysis was performed on all causes of death.

Statistical analysis

All calculations were done using SAS statistical software (SAS version 9.1.3; SAS Institute, Cary, North Carolina, USA). For all statistical analyses, *P*-values are two-tailed with $P < 0.05$ defined as significant.

Descriptive statistics. Descriptive statistics were used for age, body weight (BW), gender, SBP, all 2-D, M-mode and Doppler-derived variables, and the dosage of medications (mg/kg BW per day). Dosage of furosemide at the end of the study was also reported. Data are summarized as total range and mean ± standard deviation *(s)*. If a normal distribution could not be assumed (such as for survival time), then median and interquartile range (IQR) were used.

Kaplan-Meier analysis

Survival curves plus median and IQR survival times were obtained using the Kaplan-Meier method. Survival time was counted from the day of CHF diagnosis to the day of death. The endpoint of the study was death (all causes). Dogs which were lost to follow-up, or were still alive at the end of the study, were included in the survival analysis up until the last time point at which they were known to be alive after which they were censored in the analysis.

Univariate and multivariate Cox analyses

The association between variables and survival time was evaluated using Cox proportional hazard analysis (SAS PHREG) with right censoring. Hazard ratios (HR), 95% confidence intervals (CI), and corresponding *P*-values were calculated. First, univariate Cox proportional hazard analysis was performed on the 16 variables judged to be the most clinically relevant: age, body weight, body surface area, gender (male/female), breed [Canadian Kennel Club Standards (CKCS)], VHS, EDVI, ESVI, LA/Ao, RF, SF, presence or absence of pulmonary hypertension at onset of CHF, and daily dosages of ACEI (benazepril or enalapril), pimobendan, amlodipine, spironolactone, as well as initial and final daily doses of furosemide. Multivariate Cox proportional hazard analysis was then performed using the stepwise selection method, with and without preselection of variables with $P < 0.25$ from the univariate analysis. The goodness of fit of the multivariate models was assessed from the Akaike criterion (24).

Results

Baseline characteristics

The 21 dogs belonged to 12 breeds (1 Cavalier King Charles spaniel, 1 mixed breed, 3 schnauzers, 4 cocker spaniels, 1 Shetland sheepdog, 2 shih tzus, 1 Scottish terrier, 1 lhasa apso, 2 collies, 3 Nova Scotia duck tolling retrievers, 1 pomeranian, and 1 poodle). There were 12 males and 9 females. All dogs were in International Small Animal Cardiac Health Council (ISACHC) CHF class III. The age, weight, VHS, and SBP, as well as the echocardiographic parameters (ESVI, EDVI, LA/Ao, SF, and RF) are summarized in Table 1. Some degree of systolic dysfunction was found in 76% of the dogs, mostly mild to moderate (Table 2). Pulmonary hypertension was documented in 1 dog.

Treatment

At baseline, 9 dogs were already receiving benazepril ($n = 7$) or enalapril ($n = 2$) and amlodipine ($n = 9$). None of the 21 dogs

Table 3. Drug dosages (mg/kg BW/day) in 21 dogs with congestive heart failure secondary to degenerative mitral valve disease

	Total number	Mean	Standard deviation	Minimum	Maximum
Furosemide					
Initial dose	21	4	2.36	1.27	12.33
Final dose	8	4.80	2.39	1.27	10.7
ACEI					
Benazepril	18	0.50	0.13	0.21	0.74
Enalapril	3	0.64	0.35	0.38	1.04
Pimobendan	21	0.56	0.14	0.37	0.81
Spironolactone	21	0.86	0.29	0.42	1.71
Amlodipine	21	0.24	0.06	0.17	0.38

ACEI — angiotensin-converting enzyme inhibitor.

were receiving pimobendan prior to the onset of CHF. After the onset of CHF, all dogs received furosemide, an ACEI (18 benazepril, 3 enalapril), pimobendan, amlodipine, and spironolactone. The mean, standard deviation, and maximum and minimum dosages for these drugs are summarized in Table 3. The final dose of furosemide (at the end of the study) is also reported. Other ancillary treatments included isosorbide dinitrate in 2 dogs (9.5%), a long-acting preparation of theophylline in 1 dog (4.8%), and amiodarone in 1 dog (4.8%).

Survival analysis

The median follow-up time was 290 d (range: 1 to 917 d), with an IQR of 99 to 430 d. Altogether 11 dogs (52%) died or were euthanized during the observation period; 5 were euthanized due to worsening of CHF, 3 dogs died of heart disease, and 3 were euthanized for unknown reasons. It was assumed that most of the deaths or euthanasias were cardiac-related. Ten dogs were censored in the analysis, all of which were still alive at the end of the study. For these 10 cases, the censored survival time was calculated as the difference between July 1, 2008 and the date of CHF diagnosis.

The median survival time (MST) (from onset of CHF to death from all causes) was 430 d. The time to 75% survival was 99 d. At the end of the study 30.8% of these dogs were alive; therefore, the time to 25% survival could not be determined. The Kaplan-Meier survival plot is shown in Figure 1.

The results of the univariate analysis are shown in Figure 2. Only 1 of the 16 variables tested showed a significant association with survival: the final dose of furosemide ($P = 0.026$).

Multivariate Cox Proportional hazards model analysis was performed using the stepwise selection procedure. Since we had concerns with over-parameterization of the models, the analysis was conducted with and without preselection of variables. First, backward selection was employed using the 3 variables with $P < 0.25$ in the univariate model (LA/Ao, initial and final daily furosemide doses). This model selected a single variable (final furosemide dose) with a HR of 1.060, 95% CI of 1.011 to 1.111 and $P = 0.0159$. The Akaike criterion value was 31.2 without covariates, and 25.9 with covariates. Then, stepwise selection using all 16 variables was used. This method proved to be the best model, with 2 variables (LA/Ao and initial furosemide dose) selected and with an Akaike criterion value of 30.0 without covariates and 24.7 with covariates. Since the criterion was lower, it proved relevant to take into account covariates in the model. The HR was 3.45, the 95% CI 1.044 to 11.4 and $P = 0.042$ for LA/Ao, and HR = 1.071, 95% CI = 1.018–1.13 and $P = 0.0081$ for initial furosemide dose.

Discussion

Our echocardiographic data illustrate some aspects of the cardiac status in dogs at the onset of CHF due to MR. The quantity of mitral regurgitation, the degree of left ventricular and left atrial dilation were at least moderate, according to published criteria (20–22). The ESVI was increased in the majority (76%) of dogs in our cohort, suggesting some degree of systolic dysfunction. This is in agreement with published experimental and clinical studies (20,25,26). The ESVI has been proposed in several publications to evaluate systolic function in dogs with MR (20,27). The Teichholz method was used herein to estimate ventricular volumes, and although it has been used in other veterinary studies (20), it is derived from human geometrical assumptions, which does not make it the ideal method to use for small dogs. Calculation of volumes using the Simpson method has yielded more accurate results (27). More sophisticated methods to assess systolic function such as Tissue Doppler imaging are starting to be investigated in veterinary medicine (28). The prevalence of systolic dysfunction increases even further in large breed dogs with primary MR (20). Systolic dysfunction was not associated with a worse outcome in our study, which could be due either to the small size of our cohort, or to the limitations of the method, as discussed. Only 1 of our dogs had some degree of pulmonary hypertension (PH) at baseline. The prevalence of PH increases with the severity of MR, increasing from 3% in mildly affected dogs to 72% in very advanced cases (30).

Selection of therapy for dogs with CHF due to MR is complex and multifaceted. Furosemide alone is effective in reducing the pulmonary congestion, but will exacerbate activation of the renin-angiotensin-aldosterone system (RAAS) (1,30). The addition of ACEI to furosemide helps address some of the neurohumoral aspects of CHF. Angiotensin-converting enzyme inhibitors block the production of angiotensin II, increase bradykinin levels, and improve left ventricular compliance and skeletal muscle flow. Two large human studies (CONSENSUS and SOLVD; 31,32) have shown increased survival in human patients receiving enalapril. In dogs, enalapril decreases pulmonary capillary wedge pressure, mean and systolic pulmonary arterial pressures, and improves radiographic pulmonary edema scores in dogs with CHF due to either MR or DCM (5). Clinical improvement with respect to cough, exercise tolerance, appetite, activity, class of heart failure, and increased survival, compared with a placebo has been demonstrated in dogs for several ACEIs such as enalapril, benazepril, and quinalapril (3–5,33).

More recently, the inodilator pimobendan has become another cornerstone of CHF treatment in dogs (9–13). In the QUEST study, 260 dogs with CHF and MVD were enrolled. One group received furosemide and pimobendan ± digoxin, while the other received furosemide and benazepril ± digoxin.

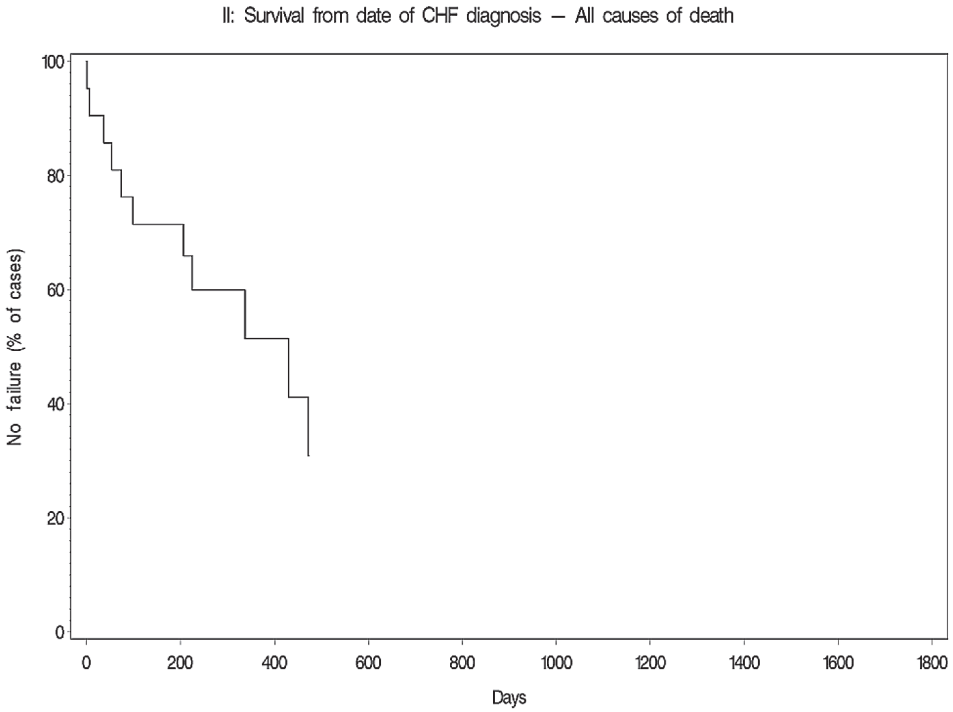

Figure 1. Kaplan-Meier plot of survival times (date of CHF diagnosis to date of death) in 21 dogs with CHF secondary to DMVD and treated with a combination of furosemide, ACEI, pimobendan, spironolactone, and amlodipine.

The primary endpoint was death, euthanasia, or treatment failure. Median survival time for the pimobendan group was 267 d, versus 140 d for the benazepril group (a difference of 91%). The pimobendan group also had a 20% absolute risk reduction of reaching the primary endpoint (13). The beneficial effects of pimobendan may derive from its positive inotropic properties which help address the systolic dysfunction, and also from its vasodilatory properties on the systemic arteries, which could potentially reduce the MR (36), and on the pulmonary arteries, which can help improve the pulmonary hypertension present in advanced chronic MR cases (29). Pimobendan can also decrease levels of norepinephrine, atrial and brain natriuretic peptides, endothelin 1, tumor necrosis factor alpha, and interleukins 1b and 6 in humans (37,38). However, in a recent study in dogs, pimobendan was unable to blunt furosemide-induced RAAS activation (39).

Spironolactone is mostly used for its antifibrotic effects via its aldosterone blocking action. In humans, RAAS inhibition by ACEIs becomes blunted after a while due to production of angiotensin II by alternate, non ACE-dependant mechanisms (14,34,35). This leads to increased aldosterone levels, mediating vasoconstriction and fibrosis. In the RALES study in humans, treatment with spironolactone was associated with a decrease in circulating levels of markers of fibrosis, and a 30% reduction in mortality compared with a placebo (14). A recent study showed that the administration of spironolactone at a dose of 2 mg/kg BW/d during a 14- to 15-month period significantly reduced the risk of morbidity/mortality by 55% compared with a placebo in dogs with CHF due to DMVD or DCM receiving conventional therapy (ACEI ± furosemide ± digoxin) (15). Note that the dose of spironolactone used in our dogs was lower (0.86 mg/kg BW/d).

Amlodipine is a calcium channel blocker, inducing arterial vasodilation, which can help to reduce the regurgitant fraction by reducing left ventricular pressure (16), in a similar fashion to hydralazine (40). Amlodipine could potentially activate the RAAS system, as shown in 1 study in which high doses were used (1.14 mg/kg BW/d). This effect was blunted by enalapril (41). In our study, lower doses were used (0.25 mg/kg BW/d) always in combination with an ACEI.

A review of the literature leads to the question: Could combination therapy including furosemide, ACEI, pimobendan, spironolactone, and amlodipine lead to longer survival survival times compared to treatment with only pimobendan and furosemide? Testing this hypothesis would require a large prospective clinical trial. However, in the absence of such a study, there may be some value in comparing the survival data from our study with data from QUEST. The cases herein were selected in order to match the inclusion criteria of the QUEST study as closely as possible. The MST in QUEST was 189 d for the composite primary endpoint, comprising the 3 separate endpoints of cardiac death (122 d), euthanasia for cardiac reasons (190 d), and treatment failure (268 d). In comparison, the MST in our dogs was longer (430 d), even though the endpoint was death or euthanasia; broader than the narrower cardiac death or euthanasia used in QUEST. None of our dogs would have fulfilled the "treatment failure" criterion of QUEST since none received daily dosages of furosemide up to 12 mg/kg BW, PO or spironolactone up to 6 mg/kg BW, PO at the end of the study. The finding of a longer MST to all-cause death or euthanasia

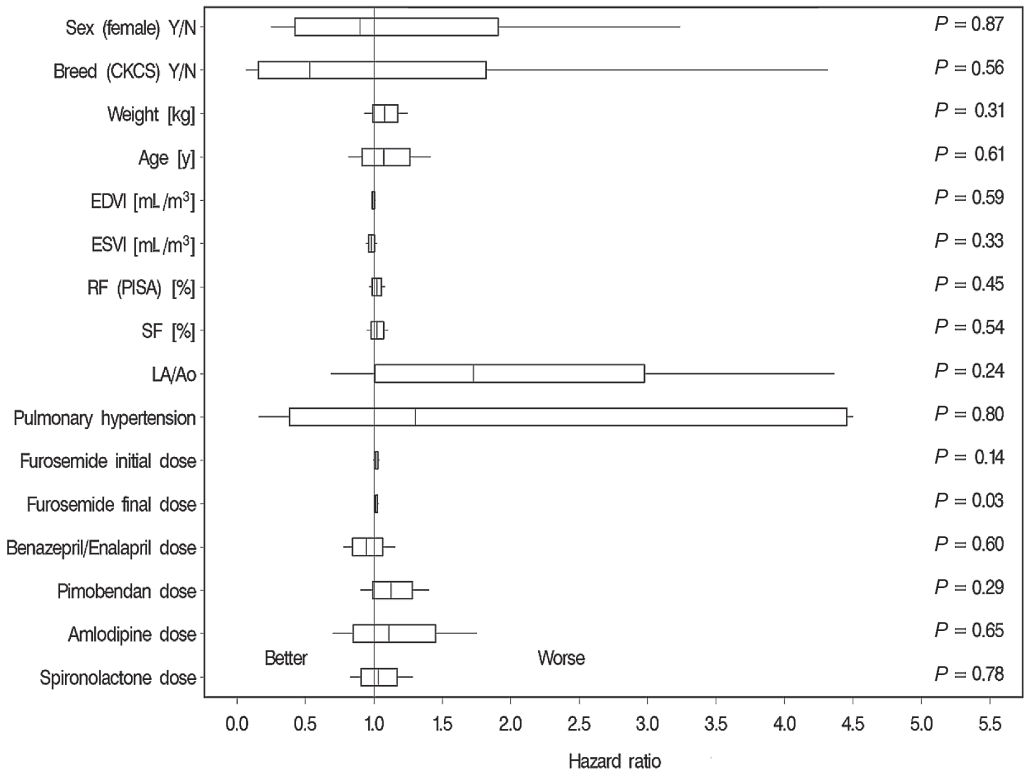

Figure 2. Graphical representation of the univariate Cox proportional hazard analysis performed in 21 dogs with CHF secondary to DMVD and treated with a combination of furosemide, ACEI, pimobendan, spironolactone, and amlodipine. Data are hazards ratios (HR) and 95% confidence intervals plus *P*-values. CKCS – Canadian Kennel Club Standards; EDVI – end-diastolic volume index; ESVI – end-systolic volume index; RF – regurgitant fraction; PISA – proximal isovelocity surface area; SF – shortening fraction; LA/Ao – left atrial to oartic diameters ratio.

of 430 d in this study compared to the MST to cardiac death (122 d) or euthanasia reported in QUEST is therefore intriguing, and warrants, in our opinion, further investigation with controlled prospective studies.

The principal limitation of this study is its retrospective nature. Therefore, biases could not be controlled as in a well-designed prospective study. In addition, the number of dogs included (21) is relatively low and only 11 (52%) dogs reached the defined endpoint of all-cause death, while 10 (48%) were censored since they were still alive at the end of the study. Censored cases weaken the power of the study The frequency of censoring in our study (48%) is similar to that reported in previous large prospective field studies conducted in dogs with ACEIs; 44% in LIVE (4) and 49% in BENCH (6) but is higher than the 25% reported in QUEST (13).

A total of 21 dogs and 11 event cases is low for survival analyses. Peduzzi et al (24) recommended not to exceed more than 1 variable per 10 subjects. Nevertheless, the data set was sufficient for 2 variables (initial daily dosage of furosemide and LA/Ao) to be identified as significantly negatively associated with survival in the multivariate analysis.

The endpoint for the survival analysis in our study was all-cause mortality. This is a robust endpoint that we consider the most clinically relevant. Previous large prospective field studies in dogs with heart failure (BENCH, COVE, LIVE, QUEST) used a combination of mortality plus treatment failure as the endpoint (3,4,6,13). Treatment failure is necessary as an endpoint in prospective studies for ethical and welfare reasons, but interpretation of results is problematic since treatment failure relies on subjective assessment by the clinician. For example, administration of concomitant treatments not allowed in the protocol is frequently used as an endpoint for treatment failure, and this is not the same as death or euthanasia.

In this retrospective study, dogs with CHF due to DMVD had long survival times (MST 430 d) when treated with a multidrug approach including furosemide, ACEI, pimobendan, spironolactone, and amlodipine. This study also provides some understanding of the degree of systolic dysfunction at the onset of CHF in dogs with DMVD. CVJ

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